What is claimed is:

1. A stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of

(a) between about 1% to about 15% of propofol;

(b) between about 1% to about 8% of a propofol soluble diluent;

(c) between about 0.5% to about 5% of a surface stabilizing amphiphilic agent;

(d) of a pharmaceutically acceptable water-soluble polyhydroxy additive that acts as a tonicity modifier; and

(e) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphlic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise,

wherein the formulation

- prevents microbial growth, defined as no more than 0.5 log increase from the initial inoculum, of each of *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 8739 and ATCC 8454), *Pseudomonas aeruginosa* (ATCC 9027), *Candida albicans* (ATCC 10231), and *Aspergillus niger* (ATCC 16403) for at least 7 days as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of a formulation at approximately 1000 colony forming units (cfu) per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viability of the microorganisms in the inoculated formulation as determined by counting the colonies of

said organism after 24, 48 hours and 7 days or other suitable length of time;

- results in little or no irritation at the site of injection as evidenced by a test wherein said composition is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 or 3 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48hrs post injection.

2. The composition of claim 1 wherein the surface stabilizing amphiphilic agent is one or more natural or synthetic surface modifiers selected from ionizable or non-ionizable phospholipids or cholesterol or a mixture of these amphiphilic agents, the total quantity of the amphiphilic agents being such that the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5 and the types and quantities of the individual amphiphilic agents are selected to provide that:

(i) the composition has a non-existent or minimum potential for hemolysis of human or animal blood, and

(ii) the irritation to the tissues at the site of injection is either non-existent or minimized, and

(iii) the composition elicits an anesthetic effect in warm-blooded animal and human subjects upon intravenous administration.

3. The composition of claim 1 wherein the propofol-soluble diluent is a synthetic or natural fatty acid, triglyceride thereof or other suitable ester or a mixture thereof.

4. The composition of claim 1 wherein the ratio of propofol to the amount of propofol-soluble diluent is from about 1:3 to about 1:0.5.

5. The composition of claim 1 wherein the ratio of propofol to the amount of propofol-soluble diluent is from about 1:2 to about 1:1.

6. The composition of claim 1 wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

7. The composition of claim 6 wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

8. The composition of claim 1 wherein the water-insoluble matrix consists of a mixture of the amphiphilic agents of claim 3 and propofol-soluble diluents of claims 4-7 and propofol.

9. The composition of claim 1 wherein the composition contains about 2% to about 10% of propofol.

10. The composition of claim 1 wherein the composition contains a pharmaceutically acceptable water-soluble polyhydroxy additive that provides the propofol containing dispersion with an osmolality of about 250 to about 700 milliosmolal.

11. The composition of claim 1 wherein the osmolality is about 300 to about 500 milliosmolal.

12. The composition of claim 1 wherein the viscosity is from about 2 to about 5 centipoise.

13. The method of reducing or substantially completely eliminating irritation upon injection of formulations containing propofol by administering a stable, sterile, and antimicrobial, aqueous dispersion of water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol as the active ingredient, up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase of the composition consisting of a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphlic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise.

14. The method of inducing anesthesia comprising administering to a subject in need of same an anesthetic inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol as the active ingredient, up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase of the composition consisting of a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphlic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise.

REFERENCES

Ardulno, M. J., Bland, L. A., McAllister, S. K., Aguero, S. M., Villarino, M. E., McNeil, M. M., Jarvis, W. R. and Favero, M. S. (1991) "Microbial Growth and Endotoxin Production in the Intravenous Anesthetic Propofol" Inf. Control Hosp. Epidem., 12(9), 535-539.

J. Babl, A. Doenicke, V. Monch (1995) "New propofol LCT/MCT fat emulsions as solvent. Approach to reducing pain on injection of propofol."Eur Hosp Pharmacy, **1**: 15-21.

Cairns *et al.* (1996) "Tolerance of mixed lipid emulsion in neonates: effect of concentration." Arch Dis Child Fetal Neonatal Ed **75**(2): F113-6.

Crowther, J., Hrazdil, J., Jolly, D. T., Galbraith, J. C., Greacen, M. and Grace, M. (1996) "Growth of Microorganisms in Propofol, Thiopental and a 1:1 Mixture of Propofol and Thiopental" Anesth. and Anal. 82, 475-478.

A.W. Doenicke, J. Babl, W. Kellermann, J. Rau, M.F. Roizen (1996) "Reducing pain during propofol injection: the role of the solvent." Anesth Analg **82**: 472-4.

A.W. Doenicke, J. Babl, U. Klotz, J. Kugler, M. O'Connor, J. Rau, M.F. Roizen (1997) "Pharmacokinetics and pharmacodynamics of propofol in a new solvent." Anesth Analg **85**: 1399-403.

A.F. Ghouri, M.A. Ramirez Ruiz, and P.F. White (1994) "Effect of flumazenil on recovery after midazolam and propofol sedation." Anesthesiology **81**: 333-339.

J.B. Glen and R. James "2,6-Diisopropylphenol as an anaesthetic agent." US Patent 4,056,635. Nov 1, 1977

J.B. Glen and R. James "Anaesthetic compositions containing 2,6-diisopropylphenol." US Patent 4,452,817. Jun 5, 1984

J.B. Glen and R. James "Pharmaceutical compositions." US Patent 4,798,846. Jan 17, 1989

D.H. Haynes "Propofol microdroplet formulations." Us Patent 5,637,625. Jun. 10, 1997.

C. B. Jones and J.H. Platt "Propofol compostion containing edetate." US Patent 5,714,520. Feb 3, 1998.

C. B. Jones and J.H. Platt "Pharmaceutical compositions of propofol and edetate." US Patent 5,731,355. Mar 24, 1998.

C. B. Jones and J.H. Platt "Pharmaceutical compositions of propofol and edetate." US Patent 5,731,356. Mar 24, 1998.

D. Mangar and E.J. Holak (1992) "Tourniquet at 50 mm Hg followed by intravenous lidocain diminishes hand pain associated with propofol injection." Anesth Analg **74**: 250-252.

R. K. Mirakhur (1988) "Induction characteristics of propofol in children: Comparison with thiopentone." Anesthesia **43**: 593-598.

Nichols, R. L. and Smith, J. W. (1995) "Bacterial Contamination of an Anesthetic Agent" New Eng. J. Med., 333(3), 184-185.

PDR (1996) "Diprivan 1% Injection" Physicains' Desk Reference 1996, p.2833.

PDR (1999) "Diprivan 1% Injection" Physicains' Desk Reference 1999.

Sandstrom *et al.* (1995) "Structured triglycerides were well tolerated and induced increased whole body fat oxidation compared with long-chain triglycerides in postoperative patients." JPEN J Parenter Enteral Nutr **19**(5):381-6.

G.E. Sklar (1997) "Propofol and postoperative infections." Ann Pharmacother **31**: 1521-3.

I. Smith, P.F. White, M. Nathanson, and R. Gouldson (1994) "Propofol – An update on its clinical use." Anesthesiology **81**: 1005-1043.

Sosis, M. B. and Braverman, B. (1993) "Growth of Staphylococcus aureus in Four Intravenous Anesthetics" Anesth. and Anal. 77, 766-768.

Sosis, M. B., Braverman, B. and Villaflor, E. (1995) "Propofol, but not Thiopental, Supports the Growth of Candida albicans" Anesth. and Anal. 81, 132-134.

Stenz, R. and Bauer, K. H. (1996) "A new physiologically approached in vitro test for quick evaluation of the hemolytic activity of surfactants" Pharmazie, 51(5), 283-287.

R.D. Stark, S.M. Binks, V.N. Dukta, K.M. O'Connor, M.J.A. Arnstein, J.B. Glen (1985) "A review of the safety and tolerance of propofol ('Diprivan')." Postgrad Med J. **61 S**: 152-156.

Tessler, M, Dascal, A., Gioseffini, S, Miller, M. and Mendelson, J. (1992) "Growth curves of Staphyloccoccus aureus, Candida albicans and Moraxella osloensis in propofol and other media" Can. J. Anaesth. 39(5), 509-511.

H. G. Weder "Propofol Nanodispersions." PCT Patent Application WO9710814. March 27 1997.

P.F. White and J. B. Negus (1991) "Sedative infusions during local and regional anesthesia: Acomparison of midazolam and propofol." J. Clin. Anesth 3: 32-39.